SUPPORT FOR THE AMENDMENTS

The present amendment amends claims 23, 27, 28 and 32.

Claims 27 and 32 have been amended to place these claims in a better condition for allowance. Support for these amendments is provided by the originally filed claims and specification.

Support for the amendment to claims 23 and 28 is found at specification page 2, lines 8-10 and 21-22, page 4, lines 22-26, page 5, lines 6-11 and 16-20, page 12, lines 1-5, Example 1, Figures 1 and 2, as well as original claims 23 and 28.

It is believed that these amendments have not resulted in the introduction of new matter.

REMARKS

Claims 23-33 are currently pending in the present application. Claims 23, 27, 28 and 32 have been amended by the present amendment.

The rejection of claims 23-33 under 35 U.S.C. § 103(a) as being obvious over Kodama '169 (U.S. Patent 6,498,169) in view of Bicknell (Tumour Angiogenesis), as evidenced by Bischoff (Journal of Clinical Investigation) and Tei (Cancer Research), is obviated by amendment, which incorporates into claims 23 and 28 the limitation that the cyclic amine compound represented by the general formula (1) inhibits vascular endothelial growth factor-A (VEGF-A).

Amended claim 23 recites, in part, a method for inhibiting angiogenesis comprising: administering to a patient in need thereof an effective amount of a cyclic amine compound represented by the general formula (1); and inhibiting vascular endothelial growth factor-A (VEGF-A) with the cyclic amine compound.

Amended claim 28 recites, in part, a method for treating a disease or pathological condition caused by angiogenesis comprising: administering to a patient an effective amount of a cyclic amine compound represented by the general formula (1); and inhibiting vascular endothelial growth factor-A (VEGF-A) with the cyclic amine compound.

Kodama '169 describes that cyclic amine compounds represented by general formula (1) exhibit inhibitory effects on endothelial cell adhesion and are useful for treating inflammatory diseases (See e.g., abstract, column 1, lines 11-18 and 40-54, column 2, lines 56-67, column 3, lines 1-49, column 118, Test Example 1, column 119, Table 1 and lines 36-44, column 20, lines 26-31). Kodama '169 describes a trihydrochloride salt of 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine and a trihydrochloride salt 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (See e.g., column 47, Example 10, and column 53, Example 13).

Bicknell hypothesizes that tumor growth may be angiogenesis dependent and describes that angiogenesis is a complex process involving many prominent sequential steps including, but not limited to, the release of proteases from activated endothelial cells, extracellular matrix (ECM) degradation, and endothelial cell migration, proliferation and alignment (See e.g., columns 1 and 2).

Bischoff describes that during angiogenesis endothelial cells degrade the ECM, then migrate, proliferate, align themselves and adhere to one another to construct and extend new microcapillaries (See e.g., page 373, column 1, lines 21-33, page 373, column 2, lines 1-8 and 30-35). Bischoff describes that aberrant angiogenesis occurs in various pathologies and diseases including chronic inflammatory diseases, solid tumors and diabetic retinopathy (See e.g., page 373, column 1, lines 7-11).

Tei describes that tumor angiogenesis is highly dependent on the action of cell adhesion molecules (e.g., integrins) mediating the adhesion of cancer cells to endothelial cells (See e.g., abstract, page 6295, column 1, last line, page 6295, column 2, lines 1-6 and 12-15).

Kodama '169, Bicknell, Bischoff and Tei, when considered alone or in combination, fail to disclose or suggest a method for inhibiting angiogenesis and/or a method for treating a disease or a pathological condition caused by angiogenesis comprising administering a cyclic amine compound represented by the general formula (1) and inhibiting vascular endothelial growth factor-A (VEGF-A) with the cyclic amine compound, as presently claimed. Therefore, Kodama '169, Bicknell, Bischoff and/or Tei fail to anticipate or render obvious to a skilled artisan the methods of the present invention comprising inhibiting vascular endothelial growth factor-A (VEGF-A) with the cyclic amine compound represented by the general formula (1).

Assuming arguendo that sufficient motivation and guidance is considered to have been provided by Kodama '169, Bicknell, Bischoff and/or Tei to direct a skilled artisan to arrive at the claimed methods of inhibiting angiogenesis and/or treating a disease or a pathological condition caused by angiogenesis comprising inhibiting vascular endothelial growth factor-A (VEGF-A) with

the cyclic amine compound represented by the general formula (1), which is clearly not the case, such a case of obviousness is rebutted by a showing of unexpected results.

As previously mentioned, Kodama '169 describes that cyclic amine compounds represented by general formula (1) exhibit inhibitory effects on endothelial cell *adhesion*. As acknowledged by the combined disclosures of Bicknell and Bischoff, angiogenesis is a *complex process* involving many sequential steps including, but not limited to, the release of *proteases* from activated endothelial cells, and endothelial cell *migration*, *proliferation*, *alignment* and *adhesion*. Vascular endothelial growth factor (VEGF) is a signaling protein involved in stimulating endothelial cell *migration* and *proliferation*.

Although some compounds inhibit angiogenesis by exhibiting inhibitory effects on endothelial cell adhesion, not all angiogenesis inhibitors exhibit inhibitory effects on endothelial cell adhesion. For example, maspin is a *protease inhibitor* that inhibits angiogenesis by exhibiting inhibitory effects on endothelial cell *migration*; vasostatin, calreticulin, prothrombin and antithrobin III are angiogenesis inhibitors that exhibit inhibitory effects on endothelial cell *proliferation*; while angiostatin and VEGI are angiogenesis inhibitors that induce *apoptosis* of endothelial cells.

In addition, not all angiogenesis inhibitors that exhibit inhibitory effects on vascular endothelial growth factor (VEGF) necessarily exhibit inhibitory effects on endothelial cell adhesion. For example, VEGF-Trap is a decoy receptor substance that inhibits angiogenesis by binding to and inactivating VEGF; bevacizumab is a monoclonal antibody that inhibits angiogenesis by binding to and inactivating VEGF; and sunitinib is a VEGF receptor tyrosine kinase (RTK) inhibitor that inhibits angiogenesis by disrupting VEGF receptor-mediated signaling. However, it is unknown whether these anti-VEGF angiogenesis inhibitors exhibit inhibitory effects on endothelial cell adhesion.

Therefore, it would not have been obvious to a skilled artisan that the cyclic amine compounds represented by general formula (1) which exhibit inhibitory effects on endothelial cell adhesion would exhibit an inhibitory effect on VEGF-A, as presently claimed.

As evidenced by the experimental data presented in Example 1 and Figures 1 and 2 of the present specification, as well as Figure A of the Declaration under 37 C.F.R. § 1.132 appended herewith, Applicants have discovered that the claimed cyclic amine compounds represented by general formula (1) inhibited angiogenesis by surprisingly exhibiting inhibitory effects on VEGF-A in accordance with the methods of the present invention.

Withdrawal of this ground of rejection is respectfully requested.

The nonstatutory obviousness-type double patenting rejections of claims 23-33 as being unpatentable over claims: (1) 15-20 of Kodama '169 (U.S. Patent 6,498,169) in view of Bicknell (Tumour Angiogenesis); (2) 13-17 of Kodama '753 (U.S. Patent 6,395,753) in view of Bicknell; (3) 3 of Kodama '620 (U.S. Patent 6,605,620) in view of Bicknell; and (4) 13-17 of Kodama '221 (U.S. Patent 6,867,221) in view of Bicknell, are respectfully traversed for the same reasons as discussed above.

Withdrawal of these grounds of rejection is respectfully requested.

In conclusion, Applicants submit that the present application is now in condition for allowance and notification to this effect is earnestly solicited.

Respectfully submitted,

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